REMARKS

Applicant sincerely thanks Examiner Kishore for meeting with Applicant's counsel, Daniel Altman and Rose M. Thiessen on October 21, 2003. The claim amendments and remarks herein are responsive to the Office Action dated September 24, 2003 and fully incorporate the Examiner's suggestions during the Interview. Claims 13-23, 25 and 39 have been canceled without prejudice, and Applicant reserves the right to pursue these claims in one or more continuing or related applications.

Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner rejected Claim 38 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not enabled in the specification. In accordance with the Examiner's suggestion, Applicant has deleted the term "preventing." In light of Applicant's amendment, Applicant respectfully submits that Claim 38 is in compliance with 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected Claims 13-40 under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicant has canceled Claims 13-23.

Applicant's Claim 34 recites that the active agent can comprise bacteria, microbes, and viral agents. According to the Examiner, "it is unclear as to how these can be active agents since they themselves cause diseases." Applicant respectfully asserts that these terms are not indefinite because bacteria, microbes, and viral agents may indeed serve as therapeutic agents, and are not simply agents of disease. Attached as Exhibit A are two articles that discuss the therapeutic value of bacteria and viruses. One of ordinary skill in the art will understand that many vaccines contain portions of the virus, bacteria or microbe to be vaccinated against, in order to induce an antibody response specific for that agent. In this way, viruses, bacteria and microbes are certainly therapeutic. Moreover, Applicant has amended Claim 34 to explicitly recite "therapeutic bacteria, therapeutic microbes and therapeutic viral agents." Support for the term "therapeutic" can be found, *inter alia*, in Applicant's specification at page 5, lines 16-23, which provides that:

> One skilled in the art will understand that the current invention is not limited to the delivery of drugs or pharmaceutical agents. Any number of

> naturally occurring or synthetic substances, including diagnostic agents ***and therapeutic materials***, may be delivered according to the current invention. These substances include, but are not limited to... ***bacteria***, ***microbes***, ***viral agents***, and the like. (Emphasis added).

Accordingly, the recitation of bacteria, microbes, and viral agents in Claim 34 is not indefinite, and Applicant respectfully submits that Claim 34 is in compliance with 35 U.S.C. § 112, second paragraph.

Applicant's Claim 24 recites a non-aqueous solvent. According to the Examiner, the meaning of a non-aqueous solvent is unclear, especially in light of Claim 34 which recites several agents that do not dissolve in non-aqueous solvent. Applicant has amended Claim 34 to explicitly recite that the pharmaceutically active agent be "soluble in said non-aqueous solvent". Accordingly, this amendment should address the apparent conflict between Claim 24 and 34, and Applicant respectfully submits Claim 24 is in compliance with 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 102(b)

The Examiner rejected Claims 13-23 and 37-39 under 35 U.S.C. §102(b) as being unpatentable over U.S. Pat. No. 5,206,219 to Desai ("Desai"). Applicant has canceled Claims 13-23 and 39, and has amended Claims 37-38 to depend from an allowable claim base, namely Claim 24. Accordingly, Applicant respectfully requests withdrawal of the § 102(b) rejection of Claims 13-23 and 37-39.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected Claims 13-40 under 35 U.S.C. §103(a) as being unpatentable over U.S. Pat. No. 5,635,206 to Ganter ("Ganter") in combination with Desai. Applicant respectfully submits that there is no motivation to combine Ganter with Desai. Moreover, even assuming that Ganter is properly combined with Desai, Ganter still does not render Applicant's claims obvious.

Embodiments of Applicant's invention are patentable over Ganter because embodiments of Applicant's method uses a single-step process which does not expose the pharmaceutical agent to an aqueous phase and which evaporates the non-aqueous solvent to produce a product that is capable of being enterically coated. Ganter, which does not even mention enteric coating, does not disclose the preparation of a formulation that is capable of forming an enteric coating that is

in contact with the proliposomal formulation, as Applicant's Claim 24 recites. Indeed, as the results below demonstrate, Ganter's process does not produce a powder. Moreover, Ganter explicitly teaches away from evaporating the non-aqueous solvent, and thus the production of a powder, by stating that:

> The proliposomes prepared *by the process according to the invention* can be stored very easily because of their high concentration and their *relatively high content of alcohol*. Ganter, col. 2, lines 65-67 (emphasis added).

Applicant has amended Claim 24 to recite the powder-like or granular nature of Applicant's proliposomal product. Amended Claim 24 now recites "combining at least one lipophilic pharmaceutically active agent with at least one phospholipid in a non-aqueous solvent to produce a *granular* proliposomal combination...".

Further, because embodiments of Applicant's invention are directed to the formation of proliposomes that are capable of being enterically coated, orally administered and forming liposomes in the gastrointestinal tract, a particle size that *exceeds* about 5-6 μm is preferred because it facilitates the coating process, oral administration and absorption. Ganter, however, *teaches away* from the production of particle sizes that exceed 5 μm. Ganter explicitly states that the proliposomes "prepared according to the invention are, as a rule, smaller than liposomes which are manufactured directly" and that Ganter's liposomes are 1-2 μm and 2-5 μm in size. Ganter, col. 3, lines 5-7; col. 3, line 67; and col. 4, line 14. Thus, by Ganter's own definition, Ganter's proliposomes are smaller than about 5 μm. This is consistent with the results provided below, which show that Ganter's method produces particle sizes that average about 3.39 μm and that Applicant's method produces particles sizes that average about 8.9 μm. Again, because Applicant's proliposomes are to be coated, a larger particle size is advantageous.

Further, although Ganter superficially discloses that the percentage of water that may be used is "0-10%", it is clear that Ganter merely discloses a broad range, in which the use of *no* water is simply not taught. Ganter does not teach or suggest the preparation of poorly water soluble drugs, in which the drug is not exposed to water during its preparation. Indeed, Ganter's example disclose a proliposomal preparation that contains 7% water. As a preliminary matter, Applicant respectfully directs the Examiner's attention to case law that holds that a claimed range, or value, that happens to overlap with a disclosed range in the prior art *is* patentable. The Federal Circuit has emphasized that an applicant may overcome a *prima facie* case of

obviousness by establishing "that the [claimed] range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *In re Woodruff,* 919 F.2d 1575, 1578, 16 USPQ2d 1934, 1936) (Fed. Cir. 1990). Moreover, "when an applicant demonstrates substantially improved results...and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary." *In re Soni,* 54 F.3d 746, 751, 34 USPQ2d 1684, 1688 (Fed. Cir. 1995).

The Examiner suggested that Applicant perform both Applicant's method and Ganter's method of preparing formulations and compare the properties of the product produced by each method. In accordance with the Examiner's suggestion, Applicant performed studies comparing Applicant's method with Ganter's method. As described below, Applicant's method produces surprising and unexpected results and shows a marked improvement over Ganter's method. Accordingly, Applicant has overcome the Examiner's obviousness rejection by showing that Applicant's claimed value (0% water) is critical because the claimed range achieves unexpected results relative to the disclosed range in the prior art.

In accordance with the Examiner's suggestion, the inventor, Dr. Guru Betageri, prepared proliposomal formulations using Applicant's method and the method disclosed by Ganter. The results of the comparison studies are shown in Exhibit B. Exhibit B is a Declaration submitted by Dr. Guru Betageri under 37 C.F.R. § 1.132.

Comparison Studies—Glyburide and Benzocaine

In the Comparison Studies, Dr. Betageri compared two exemplar drugs which are poorly water soluble—Glyburide and Benzocaine. Dr. Betageri compared Applicant's method with Ganter's disclosed method. Since Ganter disclosed a range of water from 0-10%, Dr. Betageri used about 5% water in performing Ganter's method. As the Examiner suggested, Dr. Betageri also used Ganter's method using 0% water.

For Glyburide, Applicant's method showed at least *four* separate unexpected and marked advantages over Ganter's method at 5% water *and* at 0% water. Applicant's method produced:

(1) a significantly higher yield;

(2) more effective and efficient incorporation with the lipid (as demonstrated by lower absorbance in the aqueous phase);

(3) larger particle size (which is advantageous for ease of coating and increased stability in the gastrointestinal tract); and

(4) powder-like texture (which is easier to manipulate and coat than a milky texture, and is also easier to form into a solid dosage form, such as tablets and capsules).

For Benzocaine, Applicant's method was superior to Ganter's method (at both 5% water and 0% water) in at least *three* different ways. Applicant's method produced:

(1) significantly higher yield;

(2) larger particle size (which is advantageous for ease of coating and increased stability in the gastrointestinal tract); and

(3) powder-like texture (which is easier to manipulate and coat than a solution or liquid composition, and is also easier to form into a solid dosage form, such as tablets and capsules).

Accordingly, Applicant's method provides surprising and unexpected results. Because Applicant's method does not expose the drug to an aqueous phase and evaporates the non-aqueous solvent to produce a product that is capable of being enterically coated, the quality and quantity of Applicant's formulation is markedly improved.

In view of the technical results and discussion set forth above and in the attached Declaration, Applicant respectfully requests withdrawal of the § 103(a) rejection of Claims 13-40. Claims 13-23, 25, and 39 have been canceled. Applicant submits that Independent Claim 24 is allowable. Moreover, dependent Claims 26-38 and 40-42 are also allowable because they depend from an allowable claim base and because they recite features that are independently patentable over the prior art.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected Claims 13, 16-24 and 27-28 under 35 U.S.C. § 103(a) as being unpatentable over Nakagame (U.S. Pat. No. 4,615,885) in view of Desai. Applicant respectfully submits that there is no motivation to combine Nakagame with Desai. Moreover, even assuming that Nakagame is properly combined with Desai, Nakagame still does not render Applicant's claims obvious.

Applicant has canceled Claims 13-23, and has amended Claim 24 to incorporate the limitation of Claim 25, which was not rejected by the Examiner over Nakagame. Thus, amended Claim 24 now recites "combining at least one lipophilic pharmaceutically active agent with at least one phospholipid in a non-aqueous solvent to produce a granular proliposomal combination, *wherein said pharmaceutically active agent is a poorly water soluble drug*." In light of these amendments to Claim 24, Applicant respectfully submits that Claim 24 is patentable over Nakagame alone or in combination with Desai. Claims 27-28 are also allowable because they now depend from an allowable base claim and they recite independently patentable features.

CONCLUSION

In view of the foregoing remarks, Applicant respectfully asserts that the present application is fully in condition for allowance. If any issues remain that may be addressed by a phone conversation, the Examiner is invited to contact the undersigned at the phone number indicated below.

Appropriate fees have been submitted herewith. No further fees are believed to be due. However, please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: December 18, 2003

By: _____

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